

REMARKS

The Office Action of May 18, 2011, presents the examination of claims 5-14. All of these claims remain pending. Claims 5 and 14 are amended to correct typographical errors in Greek lettering to restore such to the original text of these claims. Claims 7 and 10 are amended to conform their scope to within that of claim 5 and make them proper dependent claims. No new matter is introduced into the application by these amendments.

Claims 5-14 remain under 35 USC § 103(a) for obviousness over Tobinick '195 in view of Bertini EP '276. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants have previously argued lack of *prima facie* obviousness of the present invention. The Examiner has responded to Applicants' arguments, stating:

While the prior art suggests other molecular targets for the treatment of SCI (e.g TNF-alpha and IL-1) it does not discredit the use of IL-8 antagonists in the treatment of SCI (see eg Tonai). In fact Tobinick expressly teaches the administration of IL-8 antagonists for the treatment of SCI and provides a mechanism by which the compounds act to treat the condition e.g antiinflammatory and neuroprotective activity that ameliorates oedema and provides dosing and administration information allowing one of ordinary skill in the art to practice the method with a reasonable expectation of success.

First, the therapeutic method as presently claimed for the treatment of SCI consists of the administration of the compounds of formula (I), that act as antagonists of IL-8. In the Office Action, the Examiner rebuts Applicants' argument that IL-8 is not a pluripotent proinflammatory cytokine, such as are IL-1 and IL-6, on the basis that Tonai classifies IL-8 among cytokines at page 1064.

Applicants would like to draw the Examiner's attention to the fact that, despite different formal classifications that may occur, by carefully reading the relevant passage of Tonai it is clear that the reference fully supports Applicants' position. In fact, IL-8, differently from IL-1 and IL-6, is considered as belonging to the specific subclass of chemotactic cytokines that exert their activity through activation and chemotaxis of neutrophils.

As already explained by Applicants in their previous response, IL-8 is one of the many secondary mediators of the pluripotent cytokines and one of the many chemokines activated by them. IL-8 antagonists act by inhibiting the specific chemotaxis of polymorphonuclear cells

induced by IL-8. As a consequence, the present claims are directed to a method for treating SCI which consists in administering compounds which are **only** effective in antagonizing IL-8 induced PMN chemotaxis.

The Examiner's rejection rests on the premise, advanced via the Tobinick patent, that IL-8 antagonists can be utilized as a therapy for treatment of SCI. However, as explained below, contrary to the Examiner's opinion, the prior art at the time the invention was made teaches against and discredits the use of an IL-8 antagonist as the sole active principle for the treatment of SCI (claims 5 and 14 recite that the treatment consists of administration of the named compounds), since it teaches that the PMN chemotaxis induced by IL-8 is only one of many inflammatory pathways activated in SCI. As the other pathways are not influenced by IL-8 antagonists, the skilled artisan would not have a reasonable expectation of success that blocking only IL-8 activity could be of any therapeutic benefit.

Considering the prior art available at the time the invention was made, the sole teaching the skilled person was able to gain was that the inflammatory mechanisms following a spinal cord injury involve a number of cytokines and chemokines, among which factor IL-8 does not appear as one of the most important (see the already mentioned and submitted Taoka reference) and thus that the selective inhibition of IL-8 is not a sufficient condition for protection of SCI.

In fact, besides Taoka reporting that a non-specific blocker of leukocyte adhesion (methylprednisolone) significantly reduced motor disturbances following SCI, also Segal, already mentioned and submitted, reported that **other important proinflammatory cytokines than IL-8** were involved in the inflammatory process like IL-2, IL-6 and intercellular adhesion molecular ICAM-1 in patients with long standing SCI **as possible pathogenetic factors of the delay in the functional recovery.** (*See* also the prior art disclosure comments in the specification page 3 lines 4-17 of the instant application.)

Moreover, Applicants already submitted evidence clearly showing that, at the time of making the invention, several proinflammatory cytokines were known to be involved in the inflammatory process occurring with SCI. For example in Exhibit 3, the abstract clearly teaches that proinflammatory cytokines like TNF-alpha, IL-1 β , IL-6 are involved in the SCI, and also Exhibit 4, which **was published after Tobinick**, reporting once again the involvement of **IL-1- α , IL-1- β , TNF- α and IL-6** in the inflammatory process induced by SCI.

To the previously submitted evidence, Applicants herein add further evidence, *e.g.* Exhibit 5, confirming what is stated in the abstract of Exhibit 3. Exhibit 6 herein provided is a review **published after Tobinick** that clearly goes in the same direction as **Exhibit 4**, reporting that potent pro-inflammatory cytokines are involved in the inflammatory process occurring in SCI.

In this regard, Applicants wish to emphasize that also the Tonai reference cited by the Examiner goes in the same direction. In fact, as it comes out from a careful reading of page 1070, lines 11-33, Tonai et al. set forth that besides IL-8 also ICAM-1 plays a key role in SCI. In view of the foregoing Tonai et al., whose publication is almost **contemporaneous** with that of Tobinick, clearly teaches that for treating SCI **not only an IL-8 antagonist but at least also an ICAM-1 antagonist is necessary**. Also, the experiments carried out in Tonai show an amelioration of neurological damage after SCI by administering ONO-5046, a neutrophil elastase inhibitor which interacts with many inflammatory pathways.

As a confirmation Applicants submit **Exhibit 7**, showing that the active ingredient ONO5046 blocks activity not only of IL-8 and ICAM-1, but also of TNF-alpha and IL-6 which are well known to be involved in SCI inflammatory pathway occurring in SCI (*see* the Abstract and page 1101, left column, lines 17-19).

In view of the foregoing, Applicants respectfully assert that, contrary to the Examiner's opinion, at the time the invention was made, the prior art **did indeed discredit** the use of an IL-8 inhibitor, **as the sole active ingredient**, for the treatment of SCI.

In summary, Applicants submit that the evidence of record establishes that, **at the time the invention was made**, that is, the time relevant to determination of obviousness, the state of the art was such that the skilled artisan understood that many pro-inflammatory cytokines were known as key mediators responsible for the inflammatory processes as well as for the neurological damage in Spinal Cord Injury. Therefore, the skilled person would **not** have foreseen **with a reasonable expectation of success** that the administration **as the sole active ingredient** of an IL-8 inhibitor would have been effective for the treatment of SCI.

In the context of the above described state of the art, Tobinick does not provide any teaching allowing the skilled person to overcome the above prejudice in the prior art and suggest

the skilled person that an IL-8 antagonist can be used as the sole active ingredient for treatment of SCI. In fact, as stated in the specification of the present Application (*see* page 3, lines 17-21), Tobinick's intent is "*the treatment of a number of different pathologies, including SCI by means of antagonists of IL-1, IL-6 and IL-8*". Although Tobinick mentions IL-8 among the cytokines whose inhibition would be advantageous for the treatment of a number of neurological disorders listed in the patent and, among them also of SCI, the recitation of IL-8 is minimal and the patent is substantially directed to the use of TNF antagonists such ethanercept for the treatment of these pathologies.

Moreover, as pointed out above, several prior art references clearly taught the involvement of several cytokines in SCI. Consequently the skilled person from said references was taught away from administration of only an IL-8 antagonist, in the absence of other cytokine inhibitors, as an effective treatment of SCI. This state of the art persisted even after the issue of the Tobinick patent.

Therefore all the above references, including Tobinick, constituted a clear technical prejudice leading away from Applicants' invention.

Applicants submit that, at the time the invention was made, the only convincing suggestion of the present invention would come from actual experimental evidence demonstrating effectiveness of IL-8 antagonists, administered alone, in treating SCI. However, Tobinick did not provide any experimental data demonstrating that administration of only an IL-8 antagonist is effective in the treatment of SCI.

In addition, as Applicants have explained in their reply to the previous office Action, **IL-8 is a downstream effector of IL-1/TNF, and has a more specific and limited role in the inflammation process, namely the only inducing chemotaxis.**

In view of the foregoing, **in the absence of experimental data attesting the efficacy of IL-8 inhibitors/antagonists in Spinal Cord Injury used as the sole active ingredients, the skilled artisan, aware of the primary role of proinflammatory cytokines like IL-1,IL-6 and TNF in the SCI process, as compared to the secondary chemokine role played by IL-8 would not have seriously contemplated using IL-8 inhibitors, as the sole active ingredients, for the treatment of SCI.**

In view of the above evidence, Tobinick cannot be considered as establishing in one of ordinary skill in the art an expectation of success in treating SCI by administering only an IL-8 inhibitor. Bertini et al. describe compounds that are effective as IL-8 antagonists, but the disclosure of Bertini does nothing to dispel the lack of expectation of success in making the present invention that is presented by the state of the art at the time the present invention was made.

Thus, the combination of Tobinick with Bertini fails to establish an expectation of success in making the present invention, and therefore this combination of references fails to establish *prima facie* obviousness of the present invention. Accordingly, the instant rejection should be withdrawn.

Applicants believe the pending claims are in condition for allowance, and such favorable action is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell, Ph.D., Reg. No. 36,623, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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Attachments: Exhibits 5-7